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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,957	12/04/2001	Shoshana Paglin	AP33710 072734.0121	2771

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EXAMINER	
FISHER, LATONIA M	7

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 03/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,957	PAGLIN ET AL.	
	Examiner	Art Unit	
	La Tonia M. Fisher	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-21 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-21 is/are rejected.

7)☐ Claim(s) 22-32 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-21 are pending.

Restriction Election

Applicant's election without traverse of claims 1-21 in Paper No. 5 is acknowledged. Accordingly, claims 22-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 9-10 and 20-21 of this application. Applicant does not provide any support for or examples in the provisional application concerning methods of promoting cell death comprising contacting said cell with benzolactone enamides. Consequently, claims 9-10 and 20-21 do not receive the benefit of the earlier December 4, 2000 filing date.

Claim Objections

Claims 10, 17 and 21 are objected to because of the following informalities: Claims 10 and 21 misspell the word salicylihalamide A. The wording "an macrolide" in claim 17 appears to be a typographical error. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2, 15 and 21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The wording "the cytotoxic agent is irradiation" in claims 2 and 15 is awkward and does not particularly point out the subject matter which applicant regards as the invention. Irradiation is the act of exposing to radiation or the condition of being so exposed. See The American Heritage Dictionary of the English Language, Third Edition.

Claim 21 recites the limitation "wherein the modulator is salicylihalamide A." There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-8, 11-14, and 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altan et al., *Defective Acidification in Human Breast Tumor Cells and implications for Chemotherapy*, J.Exp.Med.,Vol. 187:10, pp.1583-1598 (1998) in view of Bechimol et al., *Functional Expression of a Vacuolar-type H+-ATPase in the plasma membrane and intracellular vacuoles of Trypanosoma cruzi,* Biochem.J., V:332, p.695-702 (1998).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 1 is drawn to a method for promoting cell death following exposure to a cytotoxic agent comprising contacting said cell with a modulator of vacuolar proton ATPase activity. Claim 3 limits the cytotoxic agent in claim 1 to radiation. Claim 4 limits claim 1 wherein the cytotoxic agent in claim 1 is a chemotherapeutic agent. Claim 5 is drawn to the method of claim 1 wherein the modulator of vacuolar proton ATPase activity is an inhibitor of vacuolar proton ATPase activity. Claim 6 is drawn to the method of claim 5 wherein the inhibitor of vacuolar proton ATPase activity is a macrolide antibiotic. Claim 7 limits claim 6 wherein the inhibitor of vacuolar proton ATPase activity used in the method is a bafilomycin A1. Claim 8 limits claim 6 wherein the inhibitor of vacuolar proton ATPase activity used in the method is a concanamycin.

Claim 11 is drawn to the method of claim 5 wherein the inhibitor is an inhibitor of vacuolar proton ATPase expression. Claim 12 limits claim 11 wherein the inhibitor of the method inhibits expression of a vacuolar proton ATPase subunit.

Claim 13 is drawn to a method of promoting cell death following exposure to a cytotoxic agent comprising contacting said cell with an agent capable of inhibiting acidic vesicular function or acidification. Claim 14 limits claim 13 wherein the cell is a cancer cell. Claim 16 limits claim 13 wherein the cytotoxic agent in claim 13 is a chemotherapeutic agent. Claim 17 is drawn to the method of claim 13 wherein the agent is a macrolide. Claim 18 limits claim 17 wherein the agent is bafilomycin A1. Claim 19 limits claim17 wherein agent is concanamycin.

Altan et al. teaches a method of promoting cell death following exposure to adriamycin, a cytotoxic agent, comprising contacting said cell with bafilomycin A1 or concanamycin A, modulators of vacuolar proton ATPase activity. See p. 1583, cols. 1-2. Altan et al. describes adriamycin as a widely administered chemotherapeutic agent, p. 1585, col. 2, lines 58-62 and p. 1586, col. 1, lines 1-2 and teaches (1) V-ATPases are multi-subunit, ubiquitous components of eukaryotic organisms that function as electrogenic proton pumps; (2) proton pumps are responsible for the acidification of intracellular compartments; and (3) such acidification is important in a wide variety of cellular events, particularly proliferation. See p. 1595, col.1, line 57 and col. 2, lines 1-10. Altan et al. discloses disrupting organellar acidification in drug resistant cells with bafilomycin A1 or concanamycin A reverses the subcellular adriamycin distribution and increases adriamycin toxicity. See p. 1596, cols. 1 and 2, lines 1-5.

Altan et al. does not specifically disclose an inhibitor of vacuolar proton ATPase expression or an inhibitor or vacuolar proton ATPase subunit expression.

Benchimol et al. discloses a method of inhibiting vacuolar-type H+-ATPase expression and inhibition of vacuolar-type H+ -ATPase subunit expression by contacting a cell with bafilomycin A1.

Thus, it would have been obvious to one having ordinary skill in the art at the time the invention was made to promote cell death following exposure to a cytotoxic agent comprising contacting said cell with a modulator of vacuolar proton ATPase activity as Applicants have done with the references before them. Applicants would have been motivated to promote cell death with an art known inhibitor of ATPase, bafilomycin A1 or concanamycin, since Altman et al. teaches that inhibitors bafilomycinA1 or concanamycin increase the toxicity of the chemotherapeutic agent adriamycin and since Benchimol et al. also disclose that bafilomycin A1 inhibits acidic vesicular function or acidification. Additionally, Applicants would have been equally motivated to use these art known ATPase modulators to promote cell death.

Claims 2 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Teicher et al. *Signal Transduction Inhibitors As Modifiers Of Radiation Therapy In Human Prostate Carcinoma Xenografts*, Radiation Oncology Investigations, 4/5, pp.221-230 (1996) in view of Furuya et al., *The Role Of Calcium, Ph, And Cell Proliferation In The Programmed (Apoptotic) Death Of Androgen-Independent Prostatic Cancer Cells Induced By Thapsigargin*, Cancer Res., 54/23, pp. 6167-6175 (1994).

Claim 2 is drawn to a method for promoting cell death following exposure to radiation comprising contacting said cell with a modulator of vacuolar proton ATPase

activity. Claims 15 is drawn to a method for promoting cell death following exposure to radiation comprising contacting said cell with an agent capable of inhibiting acidic vesicular function or acidification.

Furuya et al. teach a method for promoting cell death comprising contacting said cell with the art known ATPase inhibitor, thapsigargin. In the Furuya et al. article, Thapsigargin (TG) is taught as a sesquiterpene gamma-lactone which selectively inhibits the sarcoplasmic reticulum and endoplasmic reticulum Ca2+-dependent ATPase pumps with a 50% inhibitory concentration of approximately 30 mM. Furuya et al. also teaches that programmed death initiated by thapsigargin also inhibits intracellular acidification.

Furuya et al. do not teach promoting cell death following radiation.

Teicher et al. teach a method of promoting cell death comprising irradiating a cell and contacting said cell with thapsigargin. See p. 221.

Accordingly, it would have been obvious to one having ordinary skill in the art to promote cell death following exposure to radiation comprising contacting said cell with a modulator of vacuolar proton ATPase activity as applicants have done before them. Applicants would have been motivated to contact the irradiated cells to promote cell death since Teicher et al. teaches that while radiation therapy is very useful in the treatment of prostate cancer, treatment failure still occurs in the majority of patients with locally advanced disease. See Teicher et al. p. 221.

Claims 9-10 and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Altan et al., *Defective Acidification in Human Breast Tumor Cells and implications for Chemotherapy*, J.Exp.Med.,Vol. 187:10, pp.1583-1598 (1998) in view of Boyd et al., *Discovery of a Novel Antitumor Benzolactone Enamide Class That Selectively Inhibits*

Mammalian Vacuolar-Type (H+)-ATPases, Journal of Pharmacology and Experimental Therapeutics, 297:114-120 (2001).

Claims 9 and 20 are drawn to methods for promoting cell death following exposure to a cytotoxic agent comprising contacting said cell with a benzolactone enamide. Claims 10 and 21 limit the method of claim 9 wherein the benzolactone enamide is salicylihalamide A.

The teachings of Altan et al. cited above are incorporated herein. Altan et al. does not teach use of the vacuolar ATPase inhibitors, benzolactone enamides to promote cell death.

Boyd et al. teaches benzolacone enamides, including salicylihalamide A are inhibitors of growth of tumor cells and oncogene-transformed cell lines as they inhibit mammalian vacuolar –type (H+)-ATPases with unprecedented selectivity.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to promote cell death following exposure to a cytotoxic agent comprising contacting a cell with a benzolactone enamide as Applicants have done with the references before them. Applicants would have been motivated to promote cell death by contacting a cell with a benzolactone enamide since Boyd et al. teaches benzolactone enamides, such as salicylihalamide A, show unprecedented selectivity for mammalian versus non-mammalian V-ATPases which contrasts sharply with members of the protypical bafilomycin/concanamycin class of V-ATPase inhibitor, which indiscriminately block non-mammalian as well as mammalian V-ATPases. See Boyd et al., p. 115, col. 1, lines 33-38.

Conclusion

Claims 1-21 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to La Tonia M. Fisher whose telephone number is (703) 306-5819. The examiner can normally be reached on Monday - Friday from 9:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (703) 308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

LMF
March 21, 2003

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
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